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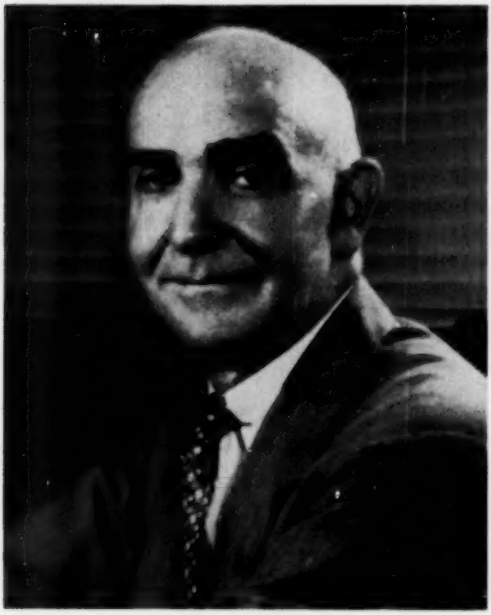

FRANK F. LAW
1894—1950
IN MEMORIAM

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American Journal of Pharmacy

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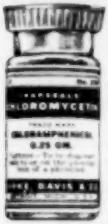

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IN MEMORIAM

FRANK F. LAW
1894-1950

PHARMACY lost one of its prominent leaders on June 5 when Frank Law died following an illness of several months.

Mr. Law was born in Edwardsville, Pennsylvania, in 1894. Following his graduation from Temple University College of Pharmacy in 1917 he enlisted in the United States Navy and went overseas with the Philadelphia Methodist Hospital Unit. He served for twenty-two months at the 1000 bed naval hospital in Brest.

Upon his return from World War I he entered the employ of John Wyeth & Brother where he worked in the various departments, gaining an insight in every phase of manufacturing pharmacy. In time he became production manager; later, vice-president and general manager and, finally, president in 1934. In 1943 the company was merged with several others and the new firm was named Wyeth, Incorporated. Mr. Law became vice-president in charge of industrial relations and pharmaceuticals and president of the Canadian subsidiary, John Wyeth & Brother, Inc., of Canada.

During Mr. Law's long years of association with the pharmaceutical profession, he held many offices in important pharmaceutical groups, and at one time served as president of the Philadelphia Drug Exchange, the oldest drug trade body in the United States. He was a member of the executive committee of the American Drug Manufacturers' Association, and was also a member of the American Pharmaceutical Association. Mr. Law was deeply interested in the alumni affairs of Temple University and was president of the General Alumni Association from 1942 through 1944. He was also a trustee of the University.

Temple University honored Mr. Law in September, 1948, by awarding him the honorary degree of Doctor of Science.

Mr. Law was known to his many friends as a genial, sincere and hard-working man. The progress and the high standards achieved by the company which he headed were in no small measure due to his guidance and leadership.

Frank Law's life is the typical story of an American boy of a humble background who through fidelity of purpose and ideals became a leader in his profession.

EDITORIAL

EARLY RESULTS OF THE "ENGLISH EXPERIMENT"

TWO years ago in an editorial titled "The English Experiment" we raised certain questions concerning the ultimate effects on pharmacy and medicine of the then new National Health Service in England. It was evident that a few of these same questions were causing some concern overseas since our editorial was reprinted in full in a subsequent issue of *The Pharmaceutical Journal*.

Recent developments in England lead us to repeat certain passages of this editorial not simply to bask in the aura of a prophet but to show some of the results of this social experiment. Two of the several questions asked previously were, and we quote, "Will the state continue to approve the use of expensive drugs or adopt a table of cheaper products?" and "Will the search for new drugs be pressed as diligently when the use of some new discovery is not likely to profit the company developing it?"

Just as was predicted, the cost of the National Health Service has continued to grow until the British government has been forced to find some means of reducing the annual outlay for this service. The ideal method, of course, would be to eliminate entirely the many thousands of abuses of the program—patients who are not ill, drugs and appliances which are not needed, and so forth. It is interesting to observe that such abuses are alleged to be quite widespread in spite of the fact that the English are probably much less irresponsible about such things than we Americans would be under similar circumstances. To rule out these and other unnecessary items of expense is a hopeless task and the only thing left to do and of course the most simple thing is to make sweeping revisions of fees and practices "across the board." We learn that the fees paid pharmacists for prescriptions have been reduced considerably by the Ministry of Health, Mr. Bevan taking such action "because of the urgent need for economy. . . ." While the way is open for arbitration this action was taken without the prior knowledge or consent of organized pharmacy in England. Still more

recently the second interim report of the Joint Committee on Prescribing has caused considerable concern, particularly to pharmaceutical manufacturers as has a letter sent to all physicians by the Ministry of Health. This letter recommends that proprietary products not be prescribed by physicians when cheaper official drugs having essentially the same action are available. It is also clear from the tone of this letter that sooner or later actual restrictions will be imposed and the physician required to adhere to a list of approved products, the need for which and the price of which is endorsed by the Ministry of Health.

On the surface such restrictions appear reasonable since indeed a table of approved products would greatly reduce product duplication and pharmacists' inventories. Detailing of "ethical specialties" would be drastically curtailed or eliminated and the physician's time saved for his patients. Everything would be streamlined for efficiency and economy—but here the bubble bursts.

If those manufacturers, who over the years have developed extensive manufacturing, control and research facilities, are no longer able to command a higher price for their quality products or to exploit their specialties then they shall not be able to compete with small, little known companies who produce cheap products since their overhead cost is low. Such small companies operate purely on a price basis; they do only a minimum of control and absolutely nothing is spent on research and development.

It is a well known fact that it is the research programs of the large concerns in pharmacy which has made available our modern, highly efficient drugs and it has been the opportunity of the successful marketing of specialties which has provided the revenue to pay for such research. If, now, such products are not to be included on the table of approved drugs the whole structure, in England at least, will collapse. Of course, government sponsored research might replace that supported by industry but it is not at all certain whether it would be as successful as the system it would replace. It seems a certainty that British drug products will find it difficult to compete in overseas markets with those products made by other companies not subject to restrictions by their home governments.

Thus we see that two of the questions which we posed two years ago have already been answered in part and in a way which makes us happy that we in America have so far escaped the toils of state

medicine. Those in our own country who still see in it the only hope for progress would do well to consider carefully some of the complications it has caused and will continue to cause overseas.

We are more than ever of the opinion that state medicine and its indispensable system of bureaucratic controls causes the stifling of initiative and retards scientific and professional progress. It is excellent political bait for the masses who like small children love those who cater to their whims and appetites regardless of the consequences.

L. F. Tice

A MICROTECHNIQUE FOR THE RAPID DETECTION OF NITRATE REDUCTION BY BACTERIA

By Louis Gershenfeld and Frank Rosolia *

W. M. Arnold and R. H. Weaver (1) presented a microtechnique for the detection of indol produced by bacteria. John Hannan and R. H. Weaver (2) introduced a microtechnique for various fermentation reactions.

In the microtechniques described by Arnold and Weaver and by Hannan and Weaver, a small quantity of medium is placed in a test tube, heated at 37°C. in a water bath and then a large inoculum of the bacterial culture is added. Thus the lag phase is decreased and a sufficient quantity of reaction product is produced in a short period of time to be detected by a suitable, sensitive, test reagent.

The purpose of this study was to determine whether a microtechnique could be used for detecting nitrate reduction by bacteria.

Experimental

Staphylococcus aureus and *Escherichia coli* were employed as the test organisms. The culture medium consisted of 3 Gm. of beef extract, 5 Gm. of peptone per liter of medium with varying concentrations of potassium nitrate. The pH was adjusted to 7.4. Sterilization was in the autoclave at 121.3°C. for twenty minutes.

The sulfanilic acid test reagent was made by dissolving 8 Gm. of sulfanilic acid in 1000 ml. of 5 N acetic acid. The alpha-naphthylamine test reagent was prepared by dissolving 5 Gm. of alpha-naphthylamine in 1000 ml. of 5 N acetic acid.

STAPHYLOCOCCUS AUREUS: Tubes containing 10 ml. of medium, with a concentration of 0.5 Gm. potassium nitrate per liter, were inoculated with a 4 mm. loopful of a 24 hour culture of the test organism. A test for nitrite was made, using 5 drops of sulfanilic acid followed by 5 drops of alpha-naphthylamine, on the first tube one hour after incubation at 37°C., on the second tube two hours after incubation, and on each succeeding tube increasing the time of incubation by

* Department of Bacteriology, Philadelphia College of Pharmacy and Science.

one hour. This was done to determine the time required for nitrite production by the method used most frequently.

In the test using the microtechnique, 1 ml. of medium was placed in a series of serologic test tubes and allowed to incubate at 37°C. in a water bath for 15 minutes; then each tube was inoculated with 2 ml. of a 24 hour culture of the test bacteria. A test for nitrite, using 5 drops of sulfanilic acid and 5 drops of alpha-naphthylamine, was performed on the first tube 5 minutes after inoculation and incubation, on the second tube 10 minutes after inoculation and incubation, and on each succeeding tube increasing the time of incubation by five minutes.

For a negative control, 1 ml. of medium was used, omitting the inoculum of bacteria and performing the test for nitrite as above. The positive control, so designated, was 10 ml. of medium inoculated with a 4 mm. loopful of a 24 hour culture of the test organism found to be positive when performing the technique in the usual manner. Here again, however, the time and method for testing for nitrite was the same as that used in the microtechnique.

The concentration of potassium nitrate in the medium was varied in an attempt to determine the concentration of nitrate which would give the most rapid production of nitrite.

ESCHERICHIA COLI: In performing the tests with cultures of *E. coli*, the same technique as used above for *S. aureus* was employed here, except that the time between inoculation and testing was reduced to one minute.

Findings

STAPHYLOCOCCUS AUREUS: The tube containing 10 ml. of medium with a potassium nitrate concentration of 0.5 Gm. per liter and a 4 mm. loopful of a 24 hour culture, gave a positive test for nitrite six hours after inoculation and incubation at 37°C.

Using the microtechnique, a positive test for nitrite was noted in fifteen minutes with media containing 1 Gm. of potassium nitrate per liter, in ten minutes using 3 Gm. of potassium nitrate per liter, in twenty minutes with 2 Gm. or 4 Gm. of potassium nitrate per liter, in fifteen minutes with 5 Gm. of potassium nitrate per liter and in ten minutes with 6 Gm. of potassium nitrate per liter. All positive (so-designated) and negative controls revealed negative findings within

these time periods. The experimental data for these tests are as follows:

1 Gm. of potassium nitrate per liter:

Time (min.)	Test	Positive control	Negative control
5	—	—	—
10	—	—	—
15	+	—	—
20	+	—	—
25	+	—	—
30	+	—	—

2 Gm. of potassium nitrate per liter:

Time (min.)	Test	Positive control	Negative control
5	—	—	—
10	—	—	—
15	—	—	—
20	+	—	—
25	+	—	—
30	+	—	—

3 Gm. of potassium nitrate per liter:

Time (min.)	Test	Positive control	Negative control
5	—	—	—
10	+	—	—
15	+	—	—
20	+	—	—
25	+	—	—
30	+	—	—

4 Gm. of potassium nitrate per liter:

Time (min.)	Test	Positive control	Negative control
5	—	—	—
10	—	—	—
15	—	—	—
20	+	—	—
25	+	—	—

5 Gm. of potassium nitrate per liter:

Time (min.)	Test	Positive control	Negative control
5	—	—	—
10	—	—	—
15	+	—	—
20	+	—	—
25	+	—	—

6 Gm. of potassium nitrate per liter:

Time (min.)	Test	Positive control	Negative control
5	—	—	—
10	+	—	—
15	+	—	—
20	+	—	—
25	+	—	—

ESCHERICHIA COLI: The tube containing 10 ml. of medium with a potassium nitrate concentration of 0.5 Gm. per liter and a 4 mm. loopful of 24 hour culture, gave a positive test for nitrite three hours after inoculation and incubation at 37°C.

Using the microtechnique, a positive nitrite test was obtained in three minutes using media containing 0.5 Gm. or 1 Gm. of potassium nitrate per liter. A positive microtest for nitrites was obtained in two minutes when the concentration was two Gm. of potassium nitrate per liter. All the controls gave a negative test. The data in tabular form are as follows:

0.5 Gm. of potassium nitrate per liter:

Time (min.)	Test	Positive control	Negative control
1	—	—	—
2	—	—	—
3	+	—	—
4	+	—	—
5	+	—	—

1 Gm. of potassium nitrate per liter:

Time (min.)	Test	Positive control	Negative control
1	—	—	—
2	—	—	—
3	+	—	—
4	+	—	—
5	+	—	—

2 Gm. of potassium nitrate per liter:

Time (min.)	Test	Positive control	Negative control
1	—	—	—
2	+	—	—
3	+	—	—
4	+	—	—
5	+	—	—

The pink color in each positive test increased with an increasing time of incubation.

Summary and Conclusions

A microtechnique for the rapid detection of nitrite produced by bacteria was developed: 1 ml. of a nitrate medium in a test tube was placed in a water bath at 37°C. for fifteen minutes. Two ml. of a 24 hour culture of the test organism were added. A test for nitrite was made by using sulfanilic acid and alpha-napthylamine.

With 10 ml. of the medium containing 0.5 Gm. of potassium nitrate per liter to which was added a 4 mm. loopful of *S. aureus* culture, a positive test for nitrite was obtained six hours after inoculation and incubation.

By the microtechnique, using 1 ml. of medium and 2 ml. of a 24 hour culture of *S. aureus* inoculum, a positive test was obtained in from ten to twenty minutes. The time required for a positive test varied only slightly with different concentrations of potassium nitrate, and a better color differentiation was obtained in those tubes which were incubated for longer periods of time. When using the microtechnique for detecting nitrate reduction by *S. aureus*, 1 Gm. of potassium nitrate in a liter of medium and a one-half hour incubation period at 37°C. are recommended.

In employing the technique using 10 ml. of medium containing 0.5 Gm. of potassium nitrate per liter and a 4 mm. loopful of *E. coli* culture, a positive test for nitrite was noted three hours after inoculation and incubation at 37°C. In the microtechnique, a positive test was obtained in two to three minutes.

When using the microtechnique with *E. coli* as the test organism, a medium containing 1 Gm. of potassium nitrate per liter and a 5 minute incubation period are recommended.

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SOME FRONTIERS IN PHARMACEUTICAL RESEARCH*

By Paul W. Wilcox **

IT is a pleasure and a great privilege to be here with you fellow pharmacists, at the annual meeting of your Association. This is not my first visit to your great country and I would guess that there are but few in the audience who have not visited the United States. If some of you have not, it is because you chose not to spend the time. There are no barriers preventing you.

To me, this cooperation between countries such as ours, need not be the subject of the well-guarded phrases of our Departments of State, but of the everyday actions of the common people living in democracies where they can think and act as they please. It is healthy for us to be able to exchange ideas freely as we are doing here today. Real progress—scientific and otherwise—is nurtured in freedom, not in dictation and dogma.

The subject of my message to you today is "Some Frontiers in Pharmaceutical Research."

It is difficult to point to an industry whose goods are as widely distributed by consumer retail outlets as are those of the pharmaceutical concerns. Another unique feature of this industry is that the products of its labor are *all* intended to prevent or mitigate disease and suffering. We now operate in a highly specialized professional form of endeavor so that the complex problems regarding drug research, development and distribution can more adequately be solved. We no longer conclude that any one pharmacist can be an expert in all phases of this profession.

The pharmaceutical research laboratory today is therefore made up of a series of scientists, each operating in his specialty with graduate training in this particular field. These areas often follow the dosage forms such as tablets, suppositories, or sterile products and sometimes overlap into the fields of medication such as antihistamines, antibiotics, antiseptics, etc.

This, to me, is a logical development and approaches very closely the trend of specialization in other professions. Lawyers are

* Presented before the Annual Meeting of the Ontario Retail Druggists Association, Ontario, Canada, June 27, 1950.

** Director of Pharmaceutical Research, Medical Research Division, Sharp & Dohme, Incorporated.

specialists in corporate, patent or admiralty law. Physicians specialize in surgery, gastrointestinal diseases or pediatrics. A typical pharmaceutical research laboratory, such as the one I represent, is therefore manned by specialists in the fields of: ointments and suppositories, tablets and granules, elixirs and tinctures, sterile solutions, physical and chemical methods of analysis, crude drugs and their extraction, lotions, colloidal solutions, etc.

On occasion another classification is used wherein the personnel is grouped into pharmacologic divisions having as their primary interest: antibiotics, sulfonamides, antiseptics, vitamins, hormones, and the like.

I prefer the former method as it is more adequate pharmaceutically, but either might be selected depending upon the particular needs of the parent organization.

In this age of specialization, a well organized pharmaceutical research laboratory is not self-sufficient. It needs the intense and daily cooperation of allied laboratories in the other divisions of medical science. As a consequence, a complete research group must include facilities and personnel in the fields of organic chemistry, pharmacology, bacteriology, nutrition, antibiotics, virology, biochemistry, immunochemistry and product development.

Scientists for such an organization must be chosen expertly. Each must know his ability and his limitations. He must cooperate wholeheartedly with his associates. Above all he must know how to *work*. He should not be burdened with the routine of ordering chemicals or apparatus, with budgets, personnel problems or other matters not directly concerned with the fundamental aims of his laboratory. He should be free to think and act under his own initiative.

Now that the facilities for work have been set up, he must choose a problem for study which is vital to the progress of pharmacy. These problems are manifold but their proper selection is often difficult. Let us enumerate a few.

The gastroenterologist has for some time been asking for an ideal *antispasmodic*. Atropine is the standard against which such compounds usually are compared. The object of research is therefore to find an orally effective drug with the antispasmodic activity of atropine but without its disturbing side effects such as dryness of the mouth, blurring of vision or an increased pulse rate. Indeed

it should be more potent than atropine in relieving certain types of muscular spasm.

When a nerve impulse is transmitted to the muscle a chemical, acetylcholine, is liberated which activates the muscle to function. The activation may be so prolonged or so great as to result in a violent involuntary contraction called a spasm. Although this reaction is not wholly understood it gives us a tool for the further study of this class of preparations. An isolated muscle strip in an appropriate bath will be activated if acetylcholine is added to the bath. When a cholinergic blocking agent such as atropine is added, the muscle ceases to function under acetylcholine stimulation.

When new chemicals are screened by a test such as this, and a compound is found having great activity, it then must be tested thoroughly in intact animals to determine whether or not it has the desired specificity of site of action; its relative freedom from the side effects of atropine and its effect in depressing the time and amplitude of contractions of the colon. Information such as this is not particularly difficult to get, but must be obtained in order to evaluate new drugs on a sound basis. Great strides are being made in the field of antispasmodics but to date we do not have the full answer to the problem.

Another interesting field of investigation which presents important research problems is that of peptic ulcer. It is generally agreed among clinicians that the secretion of acid is a necessary element in the process of ulceration. At present the principal means of combatting the acid of the gastric juice is by the use of antacids. For that purpose we have mild alumina gels, magnesium trisilicate and a few other products which neutralize small amounts of gastric acidity for only a short time. A better approach to the problem would obviously be to stop the acid from being secreted. A great deal of work is being done along this line. One laboratory has tested over 500 compounds for this purpose without success. In another laboratory, some compounds have been found which show promise.

In normal human subjects 1 mg. of atropine subcutaneously, completely abolishes basal gastric secretion, but fails to do so in a significant number of duodenal ulcer patients. In doses that can be tolerated for long periods, atropine produces only moderate depression of acid secretion in ulcer patients. As with antispasmodics, no synthetic atropine-like drug has been shown to have specificity

for inhibition of gastric secretion. Sympathomimetics and pituitrin inhibit acid secretion but their side effects are too marked to make them practical. Pyrogenic substances inhibit gastric secretion by an unknown mechanism. None of the biological extracts capable of inhibiting gastric secretion—enterogastrone, urogastrone, and histaminase—are available in sufficiently pure form for intravenous injection, the only route by which they are effective. The ideal drug when found will probably interfere with the mechanism for the formation of acid rather than with the mechanism for the excitation of the process.

In the field of *chemotherapy* there have been great advances and these perhaps have been more dramatic than those in the biological field. Two groups of agents commonly referred to as the sulfonamides and antibiotics have contributed to this success. It was about 1935 when we first heard of the sulfonamides, the so-called "wonder drugs." In 1949, approximately 2,519 tons of these compounds were produced in the United States. Sulfanilamide was the first to be used extensively. In rapid succession came similar compounds, each having more favorable pharmacologic characteristics, less toxicity, or possessing some particularly desirable antibacterial activity. Sulfapyridine was the second of the series used clinically; however, it possesses inherent toxicity and is not now widely used. Sulfathiazole, the third compound to receive attention, had several unique characteristics. Its spectrum of antibacterial activity was of great interest, but because of its rapid elimination from the body by the urinary tract, it was necessary to administer it frequently in order to maintain effective blood concentrations.

The three sulfapyrimidine compounds, namely sulfadiazine, sulfamerazine and sulfamethazine, have now largely replaced the earlier members of the series for they possess a wide range of antibacterial activity and remain in the blood stream in safe and effective concentrations for relatively long periods of time.

One of the difficulties sometimes encountered in the administration of the absorbable sulfonamides is the possibility of crystallization of these materials in the kidneys when the indicated dosage is high and the fluid intake is restricted. This crystallization may occur to a limited extent and be readily corrected by increasing fluid intake. Conversely, it may be of sufficient severity to completely block the kidney from effective function. In this case heroic surgical procedure is indicated.

Now, much of this trouble has been eliminated. It was recently found by Lehr and confirmed by others that the solubility of these sulfonamides is additive. By this we mean that when we make a saturated solution of one sulfonamide, in urine, we can dissolve in this the theoretical amount of another sulfonamide, and a third without crystallization. In other words, the solubility of one sulfonamide does not appreciably influence the solubility of others added to the same solution. Because of this, much kidney blockage has been eliminated by administering two or three sulfonamides in a dose formerly used for one, thus reducing the concentration of each sulfonamide in the urine to the point where crystallization is but a remote possibility.

Thus far reference has been made only to sulfonamides generally used for systemic effect. There is another group comprising "Sulfasuxidine," "Sulfathalidine" and sulfaguanidine indicated for the control of enteric infections. They are poorly absorbed from the gut and as a consequence are dispensed in much larger doses than the systemic or absorbable sulfonamides. These are used to reduce markedly the coliform organisms pre- or post-surgically and to take care of enteric and urinary infections.

Most surgeons use these compounds routinely in their practice to help to eliminate the possibility of peritonitis following intestinal manipulations.

In spite of this, the nonabsorbable sulfonamides are not the complete answer to the problem as sterilization of the gastrointestinal tract of man or other animals is not easily accomplished. Strides are being made in this direction, however, by combinations of the antibiotics. The administration of a mixture of Polymyxin B, Bacitracin and Streptomycin seems to show promise. Much more research needs to be done in this direction.

The other group of compounds that has been responsible for dramatic results in chemotherapy are the so-called *antibiotics*. Of these, Tyrothricin was the first to be marketed and was released initially for the treatment of bovine mastitis. It, like the more recent ones, Polymyxin B and Bacitracin, is, in general, limited to topical use either in ointment or solution form. Tyrothricin and Bacitracin are effective against gram-positive organisms only and unique in being relatively free from the criticism of causing the development of "fastness" or resistance by the organisms. Polymyxin B is also

routinely limited to topical use but is effective against gram-negative organisms.

Penicillin was the second antibiotic to receive wide and favorable reception. In 1949, the production of penicillin in the United States was approximately 98 tons. This substance may be administered locally as well as parenterally by any route. It is particularly effective against many gram-positive organisms. Since the advent of repository forms and chemical purification many of the early criticisms have been overcome.

Streptomycin, the third antibiotic to become of widespread interest, is used chiefly in the treatment of gram-negative infections. In 1949, the próduction of streptomycin in the United States was approximately 92 tons. It is used widely in the treatment of tuberculosis, influenzal meningitis, brucellosis and tularemia. One of the limitations of the use of streptomycin is the ease with which many bacteria become resistant to the drug. When given in excessive amounts this substance is not without toxic manifestations.

Aureomycin, Chloromycetin and Terramycin are rather recently recognized antibiotics that possess a very wide spectrum of antibacterial, antirickettsial and even antiviral activity. They are effective both by the oral and parenteral routes.

The administration of the antibiotics is commonly controlled by testing the sensitivity of the invading organism and selecting the appropriate antibiotic to combat this specific infection. If the organism is resistant to a large amount of the antibiotic, the dosage schedule must be rearranged to take care of it, or another antibiotic selected to which the invading organism has less resistance.

One of the chief problems of antibiotic therapy is the maintenance of effective blood levels of the antibiotic agent because of its rapid elimination from the body. When penicillin, for instance, is administered intravenously, its effective blood level seldom lasts more than two or three hours. Parenterally administered in depot form, its effects may last for two or three days. The oral administration of penicillin requires about five times as many units as does parenteral therapy. One of the disadvantages which needs to be corrected is that under these conditions the physician finds it difficult to obtain and maintain a high enough blood level to treat patients with serious infections such as subacute bacterial endocarditis or patients in which the organism has become resistant. Since ap-

proximately 80% of penicillin is excreted by the renal tubules in contrast to 20% by the glomeruli, numerous attempts have been made to enhance and prolong penicillin blood levels by the administration of various substances that suppress the tubular excretion of the antibiotic agent. The two substances, Diodrast and p-aminohippuric acid, are effective in maintaining elevated penicillin blood levels by inhibiting tubular excretion but they function on a "mass action" basis. These compounds, and penicillin, are excreted by the same specific renal tubular transport mechanism. The excretion of penicillin is suppressed because one of these compounds is present in the blood in very large amounts. There is such an excess of p-aminohippuric acid or of Diodrast in the circulating blood in comparison to penicillin that the antibiotic agent competes unsuccessfully for excretion and is maintained therefore at a higher concentration in the blood than otherwise would be anticipated if p-aminohippuric acid or Diodrast were not present.

The action of another drug, Carinamide, on the other hand, is based on an enzyme substrate competition between penicillin, which is excreted by the tubules, and Carinamide, which is refractory to excretion by this mechanism. Clinical studies have demonstrated that Carinamide, when administered orally or parenterally, suppresses the tubular excretion of penicillin regardless of the route by which the latter is administered, thereby maintaining high and prolonged penicillin blood levels. Under these conditions, Carinamide, acting as a substrate, presumably combines with an enzyme that would otherwise function as part of the mechanism for the excretion of penicillin.

This process is reversible since following the elimination of Carinamide, the enzyme is released for subsequent transport of penicillin through the renal tubules, and the antibiotic agent is then excreted in accordance with the normal pattern for renal elimination. The mode of action of Carinamide thus is concerned with selective inhibition of that essential component of the transport mechanism required for the tubular excretion of penicillin. Carinamide differs fundamentally in its mode of action from p-aminohippuric acid since it is not excreted by the renal tubules but only by the glomeruli.

Carinamide has been administered orally to patients with subacute bacterial endocarditis in a dosage of from 1.5 to 3 Gm. every three hours over periods of from 10 to 28 days, with penicillin plasma

concentrations from 2 to 20 times those anticipated when penicillin is administered alone.

As you readily can see from these statements the dosage of the drugs we have at present for maintaining high penicillin blood levels is quite large and in many cases patients would be required to take 13 to 20 Gm. per day. This treatment is wholly justified when we are dealing with resistant infections where high penicillin blood levels must be maintained. On the other hand, it is somewhat of a chore for a very ill patient to swallow so many tablets. Because of this fact, work is proceeding in the laboratories in the development of other compounds suitable for maintaining high penicillin blood levels on a much lower dosage schedule. This interesting work is showing a great deal of promise not only in the field of penicillin therapy but also for maintaining the blood levels of p-aminosalicylic acid when it is used in treating tuberculosis.

The improvement of existing dosage forms and the elaboration of available ideas in this regard could make use of all the qualified professional man-power in the field of Pharmacy for years to come. Developments in pharmaceutical research of the past have been confined largely to a relatively few laboratories. I do not believe this is necessary. When we consider the quality of the training received by those graduating from our Colleges of Pharmacy today, we cannot help but be convinced of their immense potential for good, fundamental research. Perhaps the largest percentage of this group will find its niche in Dispensing Pharmacy. This need not deter them in the least, for there are untold possibilities for properly selected research in professional stores. Some of this might take the nature of economic surveys, prescription pricing, incompatibilities, or methods of dispensing. So few papers are appearing on these subjects in current pharmaceutical literature that the practicing pharmacist finds it difficult to make progress in these lines.

Let me illustrate by a few examples.

For a century *cocoa butter* has been used routinely as a suppository base. It has value because it melts at body temperature. It can be criticized as it is a poor solvent for medication being absorbed by tissues bathed in aqueous media. It must be refrigerated. It may become oxidized and offensive on long exposure to warm air.

A few years ago the polymerized glycols became available and these compounds show great promise in this direction. They melt

above body temperature and therefore may be dispensed even in warm summer weather. They never become rancid and offensive. They are good solvents for suppository medication in general. They readily dissolve in water. One deterrent to their use is that they must dissolve in the fluid of the colon to be effective and sometimes the colon may be dry enough so that the solution is not quickly accomplished. When this happens suppositories made therefrom act as peristaltic stimulants and are evacuated. The answer to this problem may lie in combinations of these basic chemicals or the elaboration of new suppository vehicles having greater humectant properties or more rapid solubility. This is a distinct challenge to further research.

In the realm of *parenteral medication*, the vehicles most commonly employed are water and vegetable oils. Occasionally, ethyl ether, diethyl acetamide, propylene glycol and sorbitol are used. This practically completes such an available list. Obviously water is the most satisfactory of these solvents as it is physiologic in character. The medication being administered, however, is most often not physiologic and does not lend itself readily to solution in water. One way of tackling this problem is by utilizing the surface active agents which aid considerably in solubilization but these are not wholly without irritation. Another method is to resort to the injection of suspended particles. In all our work we are therefore evading the main issue, that of finding and characterizing suitable solvents for parenteral medication which will be adequate both from the pharmaceutical and the pharmacologic standpoints.

Patients on a restricted diet because of surgery or organic dysfunction are often good subjects for *intravenous feeding*. Should we become able to accomplish this readily on a large scale, these patients would logically improve at greatly increased rates. Intravenous feeding with carbohydrates has been done for many years. More recently, proteins, or their degradation products, amino acids, have been administered intravenously but the proper nutritional balance between these amino acids needs additional careful study. Fats have been parenterally administered to a few patients. This was done to radically increase their caloric intake. Special equipment for properly emulsifying such fats had to be built for this study. The fat particles in such an emulsion must be very small and the emulsion so constructed that the particles will not coalesce either before or

after administration. Here is a fertile field for pharmaceutical research.

Thermolabile drugs for parenteral use are *sterilized* currently by candle, pad or sintered glass filtration, or by tyndallization with or without bacteriostatic agents to reinforce the action of heat. Attempts have been made to make use of bactericidal gases or volatile agents which may be removed during or subsequent to sterilization. Impinging forms of energy seem to hold some promise. These may take the form of ultra-sonic sound waves as emitted by a piezoelectric quartz plate set into motion by high frequency current. These waves vibrate above the limit of audibility in the frequency range of approximately 200,000 cycles per second and are capable of fragmenting bacteria. Ultraviolet waves exert bactericidal effects but have poor penetrating properties. This deficiency can be overcome by spreading the material into a thin film as exemplified by the processes employed in destroying the infectious hepatitis virus in blood plasma. Future avenues of investigation may lie in other forms of energy, a trial of the myriad of adsorptive materials being constantly developed such as the ion-exchange resins, and lastly a combination of several methods of sterilization so as to induce a synergistic effect. This is a very important subject and deserves more of our attention.

There is so much to be done in furthering the profession of pharmacy and so little time in which to do it, that it behooves each one of us to take stock once in a while and ask ourselves what we as individuals are contributing. Are we properly selecting our research projects, or is the horizon of progress hazy? Are we setting aside a few minutes each day to decide on a plan of action which will be constructive to us personally and our profession as a group? Are we studying the literature to keep abreast of the many developments in the medicinal sciences? All this can be accomplished whether we are in the research, teaching or retail phases of our profession. Progress to the present has been made by the ingenuity, skill and brilliant leadership of a comparatively few outstanding pharmacists. The more workers in pharmacy who join in this type of action, the greater will be the progress of our profession. No longer does the physician carry the puck alone. He must have other wingmen, defensemen, a center and a goalie for support—I urge each of you to aspire to the "Stanley Cup" of pharmacy!

PHARMACOPOEIAL WANDERINGS AND HOME-COMING*

By E. Fullerton Cook

FOR more than 130 years the Pharmacopoeia of the United States has been a "child of fortune"—of good fortune, fortunately.

At last, having arrived at full manhood; vigorous, alert, effective, and with full authority and dignity, its loyal friends have provided the long-needed headquarters from which it can function with increased efficiency.

Conceived and born in New York in 1820, the Pharmacopoeia came back to its native city for twenty years of brilliant growth (from 1880 to 1901) and now, in 1950, returns to New York, once more, in full maturity.

It requires fundamental worth and an actual need for an idea and a service to continue without interruption for 130 years. So long a life also depends upon good ancestry and devoted, able and unselfish believers in its principles and policies. Such a background is the rich heritage of all Pharmacopoeias of the world, wherever they have served humanity.

Through these 130 years the U. S. Pharmacopoeia has advanced in efficiency and importance, and now justifiably looks forward to many more years of even greater usefulness.

The fascinating story of the development of pharmacopoeias from the dawn of history, as told in the brief historical sketch written by Dr. George Urdang and distributed today, tells of the efforts through the ages to prevent, or relieve, or cure the ills of men.

This has been but one phase of the service rendered by those who have devoted their lives through the centuries, unselfishly, to the welfare of humanity. To bring peace and salvation to the souls of men and to cure their bodies has always gone hand in hand, in all concepts of religion, and has been written into every code of medical practice. This spirit is perfectly exemplified in the Great Physician, Christ.

From time to time, through the centuries, groups of men have been inspired to record their medical knowledge, both how to diagnose disease, and how to identify or prepare drugs and combinations of

* Read at the dedication of the U. S. Pharmacopoeia Building, New York City, April 12, 1950.

drugs which they had found useful. The true physician and the apothecary, his professional associate, experimented and worked together and their knowledge was published for the benefit of their colleagues and for those who follow.

The names of a few of these contributors live today for those who will read: Hippocrates (375 B. C.); Galen (A. D. 130); Avicenna (A. D. 980); Vasalius (1524); Paracelsus (1541) and Valerius Cordus (1542) are but a few of these great leaders.

Physicians and apothecaries in the American colonies were intensely awake to the developments of medicine and pharmacy as practiced in Europe. Medical centres had been established in a number of the larger cities such as New York, Philadelphia, Boston, Charleston, S. C., etc. and trained apothecaries had migrated from France, Germany, England and other European countries.

The young men of the new Republic had a creative spirit and were eager to establish their own authority in all fields. In 1776 the Pharmacopoeias, published by the Medical Societies of London, of Edinburgh, of Dublin, and other European countries, were available, but there was no uniformity nor the authority to enforce these standards, so confusion existed when drugs or preparations were ordered or needed by physicians or others.

In 1778, to relieve this situation, a small book of medical formulas was compiled for use by the Military Hospital of the United States Army. This was not a general Pharmacopoeia and was limited to the specific needs of the Army. It probably was the joint product of the physicians and apothecaries enlisted in the Continental Army, both having commissioned status at that time. This volume was the first published "Pharmacopoeia" in the new country.

The College of Physicians of Philadelphia, a medical society started in 1787, took the initiative, and in 1788 appointed a committee, under the stimulus of Dr. John Morgan, to form a Pharmacopoeia for the use of the members of the College. The proceedings of the same group, in 1789, record an effort "to induce suitably qualified persons throughout the country to cooperate in the formation of a Pharmacopoeia for the United States."

While this effort failed to establish a United States Pharmacopoeia, it is evident that the subject remained one of intense interest in the Philadelphia College of Physicians through the years. It is known that Dr. Lyman Spalding of New York City, the founder of

the U. S. Pharmacopoeia, visited Philadelphia in 1809 and became a close friend of Dr. Benjamin Smith Barton, the world famous physician and botanist, who had long advocated a U. S. Pharmacopoeia which would include the new American medicinal drugs. Dr. Barton, in 1798 and again in 1804, presented papers on our native drugs and wrote "They should have a place in the Pharmacopoeia of this country, when such a desideratum shall be supplied." It has been suggested that Dr. Spalding's visit to Philadelphia may have given him the idea of a U. S. Pharmacopoeia. Certainly, when the plan matured in 1817, under the inspirational leadership of Dr. Spalding, the Philadelphia physicians were among the most enthusiastic supporters of the program, and presented a draft of a Pharmacopoeia, through their delegates, to be considered at the 1820 Convention, in Washington. They also helped to maintain and develop the U. S. P. at that time and through all subsequent years.

In 1805, the Massachusetts Medical Society also proposed the establishment of a United States Pharmacopoeia and, to give it substance, published, in 1808, their own Pharmacopoeia. This was largely based on the then current edition of the Pharmacopoeia of Edinburgh

The Massachusetts Committee actively promoted the adoption of their Pharmacopoeia for national use, for in the records of the Medical Society of South Carolina is the statement that on August 8, 1808, the Massachusetts Medical Society submitted to them a draft of a Pharmacopoeia for review. The South Carolina Society gave general approval, and suggested the "concurrence of different States in the formation of a general work of this kind." They also offered specific suggestions for improving the Massachusetts Pharmacopoeia.

The Medical Society of South Carolina had issued a pamphlet as early as 1798 giving instructions for collecting and preparing medicinal plants native to their State, "looking toward the establishment of an independent materia medica."

The New York County Medical Society also had long recognized the need for standards and uniformity in medicinal agents, and in 1816 the Physicians and Surgeons of the New York Hospital issued a Pharmacopoeia which soon received more than local popularity. It followed the contemporary edition of the London Pharmacopoeia and four years later became the basis for the first U. S. Pharmacopoeia. Dr. Samuel Latham Mitchill, then one of the most famous physicians of New York City, later President of the first U. S. P.

Convention (also a close friend of Dr. Spalding), was a member of the Committee which prepared this New York Pharmacopoeia.

On January 6, 1917, Dr. Spalding presented a plan before the New York County Medical Society for establishing a national pharmacopoeia and a committee was appointed to carry through the project.

Travel conditions were so difficult at that time that it was suggested that physicians in four sections of the Country (Northern, Middle, Southern and Western) meet, formulate their ideas, and send delegates to a national convention to be held in Washington, D. C., on Janary 1, 1820.

On June 1, 1819, eleven delegates met in a district meeting in Boston and on the same day the group of the Middle District met in Philadelphia, with nineteen delegates present. It is interesting to note that Dr. Spalding, from New York, was among those present. Both of these groups continued their session for about a week and prepared drafts of pharmacopoeias to be submitted to the Washington Convention. The Southern group held no meeting, but arranged for delegates to go to Washington.

Dr. Spalding, in a letter still extant, writes of the difficulties he had to overcome to attend the U. S. P. Convention of 1820. Not having access to railroad time tables, Dr. Spalding, in New York, wrote to his Congressman in Washington to learn how best to travel from New York City to Washington. The reply suggested that he leave New York at 11 A. M., in "The Olive Branch," a mail stage, sleep at Trenton that night, and continue the next day, reaching Philadelphia at 10 the next morning and Baltimore by 2 or 3 the following morning. At 6 A. M. the stage left Baltimore and was scheduled to reach Washington about 12 noon. The trip required from 49 to 50 hours.

The First U. S. P. Convention opened on Saturday morning, January 1, 1820, in the Senate Chamber of the Capitol at Washington. Delegates were there from New Haven, Philadelphia, Washington, Delaware, New York, Baltimore and Georgia. They remained in session for about a week, during which time the first draft of the Pharmacopoeia was prepared. Before adjourning, a committee of five was appointed to complete and publish the book, and Dr. Spalding was elected Chairman. The Committee held three meetings during the next few months, and the first U. S. Pharmacopoeia appeared December 15, 1820.

Mention is made of the Pharmacopoeia Committee meeting in Dr. Lyman Spalding's house in New York, so it is fair to assume that this was the first editorial office of the U. S. Pharmacopoeia. His address at that time was 81 Beekman Street. This is close to what is now the entrance to the Brooklyn Bridge, which then, no doubt, was the centre of residential New York City.

In the founding of our Republic we were blessed by the leadership of truly great men. They had high ideals, wide vision, and great wisdom. The Preface to this First U. S. Pharmacopoeia established the firm foundation upon which rests the U. S. Pharmacopoeia of today and the principles there set forth are the backbone of the Fourteenth Revision of the U. S. Pharmacopoeia of 1950. The 1820 Preface starts—

> "It is the object of a Pharmacopoeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage. It should likewise distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries.
>
> "The value of a Pharmacopoeia depends upon the fidelity with which it conforms to the best state of medical knowledge of the day. Its usefulness depends upon the sanction it receives from the medical community and the public; and the extent to which it governs the language and practice of those for whose use it is intended. . . ."

Following the plan proposed by the 1820 Convention for the revision of the U.S.P. every ten years, Dr. Mitchill, the President of the 1820 Convention, sent a letter in 1828 to the incorporated medical societies and schools of the United States, inviting each of them to appoint three representatives to attend a Pharmacopoeial Convention to be held in Washington on January 1st, 1830.

Through a misunderstanding, some of the delegates met in New York City, while others assembled in Washington, resulting in two Conventions and two U. S. Pharmacopoeias of the 1830 period.

At the 1830 Washington Convention, in addition to the regular delegates, the Surgeon General of the Army, the Senior Surgeon of

the Navy, and the medical members of Congress were invited to participate. Dr. Thomas T. Hewson of Philadelphia was elected revision Chairman.

In 1830 Dr. Hewson's home in Philadelphia was on Walnut Street, above 9th Street, so we now locate the second editorial office of the U. S. Pharmacopoeia.

The New York Pharmacopoeia of 1830 was not continued, and the Washington Convention again met in 1840 with increased attendance and interest. Dr. George B. Wood of Philadelphia was elected Chairman of the 1840 Committee of Revision, and in this Revision, on invitation, the colleges of pharmacy of Boston, New York and Philadelphia took a prominent part in the drafting of formulas and new preparations. The French Codex, which appeared about this time, provided much stimulating new material.

Dr. George B. Wood continued as Chairman of the U.S.P. Revision Committee for two decades, 1840 and 1850, and his home and office in Philadelphia were successively at 1921 Mulberry St. (1840), and 419 Mulberry Street (1850).

Many years later, Professor Remington recounted an incident of his boyhood, probably about 1855; he was passing Dr. Wood's home and some papers blew out of the window. He collected them, rang the doorbell and the elderly Dr. Wood himself came to the door and, taking the papers, said something to this effect: "My boy, you have been very kind. Perhaps some day you too will be working on papers of equal value." Strange indeed that Remington should have been Dr. Wood's successor almost fifty years later.

Dr. Franklin Bache of Philadelphia, the grandson of Benjamin Franklin, was elected Revision Chairman by the 1860 U.S.P. Convention.

At the 1870 Convention, Dr. Joseph Carson, one of the outstanding physicians in Philadelphia of that period, was elected Chairman of the Revision Committee. His home was at 1117 Spruce Street. This house still stands, a substantial four-story, red-brick house with white marble steps and wrought iron rails.

The decade from 1870 to 1880 brought into the Pharmacopoeia picture new, vigorous and forceful characters. The men who had carried the major responsibilities for more than 50 years had died or were retiring, and medical and pharmaceutical knowledge was rapidly advancing.

Dr. E. R. Squibb, Dr. Frederick Hoffmann, and Dr. Charles Rice, of New York, Dr. Horatio C. Wood, Sr., Prof. John M. Maisch, and Prof. Joseph P. Remington of Philadelphia, Prof. C. Lewis Diehl of Cincinnati and many others became prominent. Dr. Squibb personally made many suggestions for the revision of both the pharmaceutical and chemical texts, and Dr. Charles Rice became the Chairman of a Committee about 1876 of the American Pharmaceutical Association which developed many new ideas for the next Pharmacopoeia of 1880.

The outstanding ability of Dr. Charles Rice was now widely recognized and he was elected Chairman of the U.S.P. Revision Committee of 1880 and again reelected in 1890 and 1900. Numerous accounts of the life and accomplishments of this remarkable man have been written, but time does not permit their elaboration here. The results, however, speak for themselves, for the U.S.P. of 1880 was a revolutionary volume and has been the model in style and arrangement for all subsequent revisions of the U.S.P. Instead of giving working formulas only, which had been the chief characteristic of previous Pharmacopoeias, the 1880 book contained many standards, tests and assays for the finished official products.

Dr. Rice, educated in famous universities of Europe, and a master of a score of languages and of the science of his day, was the chief analyst and pharmacist for the Bellevue Hospital in New York City. There, in his laboratory and library, he wrote and issued the U.S.P. Revision Circulars, many in his own handwriting, and edited the Pharmacopoeia for two decades. Though ill in 1900, Dr. Rice was again elected to the Chairmanship of the Revision Committee, but was able to do little work on that Revision before his death in 1901.

On the death of Dr. Rice, Prof. Joseph Price Remington, who had been Vice-Chairman of the Revision Committee since 1880, was elected Revision Chairman and proceeded actively with the Eighth Revision. Prof. Remington was the Professor of Pharmacy at the Philadelphia College of Pharmacy and his home in the winter was at 1832 Pine Street, Philadelphia, and in the summer at Longport, N. J.

These two homes became the centre of Pharmacopoeial work. Here conferences were held, U.S.P. correspondence and revision circulars issued, editorial work done, and laboratory experiments conducted.

It was my privilege to be one of the College assistants as well as the personal assistant to Prof. Remington at that time, and when the boxes containing the U.S.P. records and equipment arrived from Dr. Rice's office in New York, to help unpack, examine and store the material, and later to help prepare the first U.S.P. Revision Circular issued from the New Chairman's office in Philadelphia. The Pharmacopoeia soon took possession of Prof. Remington's home at 1832 Pine Street. The double library, the billiard room, the third floor laboratory, and Prof. Remington's bedroom were all used. The shipment, by freight, of all necessary equipment, records, and library to Longport and back each summer for sixteen years—there were always 25 or more barrels to be packed and headed—was no small part of the job each spring and fall. At Longport a two-story building containing a billiard room, laboratory and bedrooms, previously used by Prof. Remington's three sons, was turned over to the U.S.P. and became known to all on the Revision Committee and Board of Trustees as the "Pharmacopoeia Factory."

Prof. Remington became ill in 1917, and died in January, 1918. Prof. Charles H. LaWall, Prof. Remington's other College assistant and at that time a member of the Revision Committee, was elected Revision Chairman for the interim period until 1920. Prof. LaWall used his private laboratory which was near the College, at 7th and Race Streets, as the U.S.P. office and, when the present Revision Chairman was elected at the 1920 Convention, he rented a small section of Prof. LaWall's Laboratory for U.S.P. revision work but, in 1927, when the new buildings of the Philadelphia College of Pharmacy and Science were erected at 43rd and Kingsessing Avenue, the College immediately offered office facilities for the Pharmacopoeia, and the U.S.P. Revision offices remained there as the guest of the College, without charge for space, janitorial service, heat or light until 1945, almost 20 years.

During the decade from 1930 to 1940, when for several years the revision of the Food and Drug Act was before Congress, Mr. Walter G. Campbell, Commissioner of the Food and Drug Administration, frequently spoke to the Revision Chairman of the desirability of having a more stabilized organization, with permanent headquarters and staff for the Pharmacopoeia. He felt that its quasi-legislative status, under the Food and Drugs Act, would be strengthened and stabilized by such a development. This was an important factor back of the

proposal to the 1940 Pharmacopoeial Convention to establish independent and permanent headquarters for the Pharmacopoeia.

The 1940 Convention recognized that the time had come to provide Pharmacopoeia headquarters, entirely independent of all other interests, and fully under the control of the Board of Trustees, and gave authority to the Board to provide adequate Pharmacopoeia offices.

The war delayed this program, but a temporary move was made in 1945 when the Board bought a small office building in Philadelphia, near the Philadelphia College of Pharmacy and Science, where several members of the U.S.P. staff were teaching. The U.S.P. records were transferred from the College to this temporary building and the office and staff were organized on a more stable basis.

In the meanwhile, the Board continued its efforts to find a permanent location for the Pharmacopoeia, and numerous buildings were investigated in both Washington and New York City. Eventually, the modern building at 46 Park Avenue in New York City was brought to the Board's attention, and its central location, superior constructions, and many other advantages, including the reasonable price for which it could be bought, persuaded the Board to purchase the building now being dedicated.

The service which the U.S.P. renders today, and has rendered for 130 years, has stimulated voluntary cash contributions from many friends. We hope these gifts will eventually cover all costs of this building and thus make it a gift to the Convention. This response speaks for the appreciation and widely recognized need for continued and even more efficient service from the U. S. Pharmacopoeia for many decades to come.

The strategic location of the building, within easy walking distance of air and rail terminals in New York City, is of special importance since many of the revision and research programs of the Pharmacopoeia today require frequent conferences with government officials and with professional and technical experts from universities and private and industrial organizations, whose representatives come from distant points and often for only a day's conference.

President Eggleston, I have been requested to speak for the Board of Trustees on this occasion and to turn over to you, as the representative of the United States Pharmacopoeial Convention, our

official corporate body, the new Pharmacopoeial Headquarters, at 46 Park Avenue.

We trust that the life of the Pharmacopoeia in New York City will be long and uninterrupted and will demonstrate continued efficiency, broadened service, and unprecedented progress.

With continued professional integrity of the high order maintained in the past, with ideals untarnished, and with services always concentrated basically upon the high calling of preventive and curative medicine, the Pharmacopoeia stands on a firm foundation with a safe and useful future assured.

SELECTED ABSTRACTS

Antrycide in the Treatment of Trypanosomiasis. F. H. S. Curd and D. G. Davey. *Brit. J. Pharmacol. 5*:25 (1950). The principal object of the study conducted by the authors was to find a drug which would be effective against the cattle trypanosomiasis so prevalent in Africa. It is estimated that as much as four and one half million square miles of tropical Africa are retarded from full development because of the prevalence of this disease among cattle, the most deadly form caused by *Trypanosoma congolense*.

Working from previous products studied the authors eventually synthesized the quinoline-pyrimidine substance known as antrycide. Two salts were used in the experiments, the dichloride and the dimethylsulfate. Both are white crystalline solids. The halide is sparingly soluble in water but the dimethylsulfate is soluble up to 33 per cent.

Toxicity studies performed on mice indicated that the salts were both toxic to about the same degree when given intravenously. The LD_{50} was about 10 to 15 mg. per Kg. of body weight. When administered subcutaneously or intramuscularly the methylsulfate salt was less toxic but still quite so whereas the chloride was very slightly toxic. Further studies indicated that the toxicity effects were directly related to the amount of drug in solution, and not to the amount in suspension when administered subcutaneously or intramuscularly.

Therapeutic experiments performed on mice showed that the chloride and the methylsulfate were equally effective. The authors stated that a difference could be expected in larger animals for the dose was so small in mice that even the chloride could be given as a solution rather than as a suspension. The drugs were given by subcutaneous injection, as a single dose, within 48 hours after infection. Mice which remained free of apparent infection for 30 days after treatment were regarded as cured. The drugs proved to be most effective against *T. congolense*, *T. evansi*, *T. equinum*, and *T. equi-*

perdum but produced a marked effect against *T. brucei*, *T. rhodesiense*, and *T. gambiense*. No activity was evident against *T. cruzi*. As little as 1.25 mg. per Kg. cured all 40 mice infected with *T. congolense* while it required 25 mg. per Kg. to cure all 8 mice in a group infected with *T. rhodesiense*. The authors compared the results with other drugs and found that antrycide has the widest range of activity against the various species of trypanosomes of any drug known. Prophylactic experiments showed that the chloride prevented infection for several weeks. The authors concluded that the prophylactic properties of antrycide are due to the establishment of a reservoir of the less soluble chloride beneath the skin from which absorption takes place slowly.

The authors pointed out that the greatest service in the control of cattle trypanosomiasis will be rendered by a drug which not only cures an established infection but confers protection against further infection. In mice antrycide provides this protective effect when the chloride is injected subcutaneously or intramuscularly, due to poor absorption rather than slow excretion.

The Effect of Aureomycin on the Intestinal Flora of Man. W. H. Dearing and F. R. Heilman. *Proc. Staff Meet. Mayo Clinic* 25:87 (1950). The effect on the bacterial flora of the intestinal tract of man of aureomycin, succinylsulfathiazole, Sulfathalidine and dihydrostreptomycin as a means of preoperative control was studied by the authors. A group of 148 unselected hospitalized patients with various intestinal lesions were used as the subjects.

A series of saline enemas were administered and then oral treatment was begun. In the first group 250 to 750 mg. of aureomycin were given four times a day. The authors stated that of the 66 persons treated with 750 mg. of aureomycin per dose the smears were seldom Gram positive but were frequently Gram negative. *Escherichia coli* were cultured in only 7 instances, *Streptococcus faecalis* in 4 and *Aerobacter aerogenes* in 1. Yeasts were frequently cultured but spores were never found. In the second group the 39 patients were treated with 4 Gm. of succinylsulfathiazole or sulfathalidine 6 times for the first day and then 2 Gm. 6 times a day or with 500 mg. of dihydrostreptomycin four times a day, all orally. Smears from this

group showed heavy growth of both Gram positive and Gram negative bacteria. *E. coli, S. faecalis* and spores were usually present, *A. aerogenes* was found in 4, and yeasts in 3. The dihydrostreptomycin was effective initially but resistant strains developed rapidly.

Thus it would appear that aureomycin holds promise as an effective agent for the preoperative treatment of patients about to undergo abdominal surgery.

Preliminary Clinical Evaluation of the Anesthetic, Surital Sodium. M. Helrich, E. M. Papper, and E. A. Rovenstine. *Anesthesiology 11*:33 (1950). Surital Sodium (sodium 5-allyl-5-(α-methylbutyl)-2-thiobarbiturate) was administered intravenously in normal saline to 1200 patients ranging in age from 3 to 93 years in various surgical procedures. A 0.3 per cent solution was infused for hypnosis with regional anesthesia, a 2 to 2.5 per cent solution was injected intermittently to induce cyclopropane or ether anesthesia, for induction and endotracheal intubation and as an anticonvulsant during hyperthermia, and either concentration was used for complete anesthesia. The drug was used alone if the anesthesia was to last for not more than 20 minutes and with nitrous oxide-oxygen for longer periods.

Curare was also administered in several cases in order to increase muscular relaxation.

The authors reported that the various durations of anesthesia ranged from 3 minutes to 6 hours. In 9 per cent of the patients hypotension with little or no change in pulse rate was noted, 4 per cent experienced severe and 11 per cent some respiratory depression, 2 per cent experienced severe and 6 per cent some laryngospasm, and 5 per cent experienced excitement during induction. Emesis occurred in only 1 patient, 2 of 4 asthmatic patients experienced attacks after the administration of the anesthetic, and one elderly patient with carcinoma of the esophagus and trachea died of asphyxia resulting from the drug. The authors concluded from their observations of this rather large group of patients that Surital Sodium seemed to provide more rapid awakening from a comparable plane of anesthesia and a more rapid restitution of spontaneous breathing after the rapid administration of large doses than similar drugs in use at the present time.

The Antagonism of Dicumarol by Vitamin K Preparations. R. Miller, W. Harvey, and C. Finch. *New England J. Med. 242*:211 (1950). Dicumarol was injected intraperitoneally in 80 rats in doses of 5 mg. These doses prolonged the prothrombin time from a normal of 13 to 15 seconds to an average of 35 seconds 24 hours later. However, the concomitant injection of 5 mg. of vitamin K_1 or K_1 oxide reduced the prothrombin time at the 24 hour period to 15 to 20 seconds, but 5 to 50 mg. of water soluble vitamin K derivatives, Hykinone (menadione bisulfite) or Synkayvite (2-methyl-1,4-naphthalenediol diphosphoric ester tetrasodium salt), resulted in prothrombin times of 19 to 35 seconds at the 24 hour period. Control rats given 20 mg. of dicoumarin died of pericardial hemorrhage. Groups of the animals given the same dose of dicoumarin and 20 mg. of Hykinone or Synkayvite likewise succumbed or, the few that survived showed greatly prolonged prothrombin times. However, rats given 20 mg. of dicoumarin and 5 to 20 mg. of vitamin K_1 or K_1 oxide survived and the prothrombin times were 15 to 35 seconds.

The authors reported that the results obtained experimentally with dogs were similar to the results obtained with rats. Doses of 6 to 1000 mg. of Hykinone and Synkayvite had no effect in reducing the prothrombin time, either intravenously or orally. Doses of 1000 mg. of Hykinone and of more than 250 mg. of Synkayvite were found to be toxic in dogs.

The results obtained in human beings who were stabilized on oral or intravenous doses of dicoumarin ranging from 50 to 150 mg. a day were similar to those found in the experimental animals. Both vitamin K_1 and K_1 oxide were effective in reducing the prothrombin times and were non-toxic in doses of 500 to 1000 mg. while the soluble salts were ineffective in doses ranging from 64 to 1000 mg.

Intravenous Iron Therapy in the Treatment of Microcytic Hypochromic Anemia. A. S. Ramsey. *Brit. Med. J.* No. 4662: 1109 (1950). There are a number of patients afflicted with microcytic hypochromic anemia who have taken oral iron preparations for long periods of time without any apparent benefit. In a few cases there are diseases and deficiencies present which could account for

the continuation of the anemia. In the other cases the patients have not been able to tolerate effective doses of iron by mouth or they apparently have not been able to absorb adequate quantities.

Previous experiments have indicated that injected iron is used almost quantitatively for the formation of hemoglobin. Unfortunately, most preparations, even in very small doses, produce severe toxic effects. First noticed in animal experimentation and later tested in human beings, it was found that the injection of saccharated iron oxide did not cause reactions and that it was completely utilized in hemoglobin synthesis.

Three case histories were given by the author as typical of those treated by the intravenous injection of saccharated iron oxide. In each case there was a prompt and steady increase in the hemoglobin and in the 2 patients having a low RBC count there was also a rise in this respect. The iron cannot be given in one massive dose without producing severe side effects. The most pronounced side effect was severe nausea and vomiting. Several of the patients were confined to bed for several hours but all gradually recovered, following the reactions arising from the injection of massive doses of iron. However, if treatment is begun with daily doses of 100 mg. of iron and then gradually increased to 200 or 300 mg. the toxic reactions can be avoided. Antihistaminic drugs were of no value in reducing the incidence of toxic reactions.

Investigations have shown that the iron oxide is taken up by the reticulo-endothelial cells lining the vascular channels particularly in the liver and spleen. The metabolic activity of these cells then converted the iron into a soluble form which is released into the blood plasma in loose combination with the plasma proteins. In this form it is capable of passing through the capillary walls and being stored in the lymphatic nodes and parenchyma cells of the liver and kidney until converted into hemoglobin.

The side reactions which occurred in the patients given massive doses of iron closely resembled those that occur in patients with paroxysmal hemoglobinuria from cold. The suggestion is offered that the reaction in both conditions may be caused by a sudden increase in activity of the reticulo-endothelial system. If this proves to be the answer the author stated that it is unlikely that any preparation of iron will be found which would allow treatment of anemic patients with a single injection of the calculated dosage requirement.

BOOK REVIEWS

Evaluation of Chemotherapeutic Agents. Edited by Colin M. MacLeod. 205 pages; Columbia University Press, New York. 1949.

This book consists of a series of papers presented at a symposium held at the New York Academy of Medicine on March 25 and 26, 1948.

The titles of the fourteen papers presented seem the best means of describing its contents. These were:

1. The Significance of Drug Concentration in the Blood, as Applied to Chemotherapy.

2. Blood Levels, Renal Clearance, and Chemotherapeutic Activity, With Particular Reference to Arsenicals and Penicillin.

3. The Binding of Chemotherapeutic Agents to Proteins and Its Effect on Their Distribution.

4. The Problem of Microbial Resistance to Chemotherapeutic Agents.

5. Defense Mechanisms of the Host in Relation to Chemotherapy of Acute Bacterial Infections.

6. The Nature of the Lesion and the Response to Antimicrobial Therapy.

7. Transcutaneous Antibiotic Therapy of Localized Soft Tissue Infections.

8. Chemoprophylaxis of Meningococcal Infections and of Bacillary Dysentery.

9. An Evaluation of Chemoprophylaxis of Streptococcal infections.

10. Evaluation of Antimalarial Drugs.

11. The Chemotherapy of Rickettsial Diseases.

12. Chemotherapy of Viral Infections.

13. The Experimental Evaluation of Chemotherapeutic Agents in Cancer.

14. The Clinical Evaluation of Chemotherapeutic Agents in Cancer.

Each paper was prepared by a well-known worker in his respective field and the published series should prove of interest to research workers and clinicians alike.

L. F. Tice

The Canadian Formulary 1949. Seventh Edition. Prepared by The Canadian Conference of Pharmaceutical Faculties; xiii + 96 pages incl. index. University of Toronto Press.

This most recent edition of the Canadian Formulary was prepared by a number of sub-committees selected from the Canadian Conference of Pharmaceutical Faculties. This is the first edition prepared exclusively by this group, previous editions having been prepared by several other bodies including the Ontario College of Pharmacy which originated this compilation in 1905.

The book contains in its main section a number of pharmaceutical formulas representing preparations which are extensively used in Canada. Complete directions for manufacture are given in each instance. Following these are a number of appendices. Appendix I gives the standards for ingredients used in the preparations where such ingredients are not official in the British Pharmacopoeia. In many cases the C. F. standards are simply listed as those of the U.S.P. XIII or the N. F. VIII. Subsequent appendices include: abbreviations, imperial-metric equivalents, buffers and buffered solutions, isotonic solutions, vehicles and veterinary doses.

The formulas given seem to have been selected with care and good pharmaceutical technic is evident in the directions given. The section on vehicles is based on taste acceptance tests conducted by the Sub-Committee on Vehicles. It is unfortunate that the material on isotonic solutions does not take cognizance of studies over the past several years which show the freezing point of tear fluid to be identical with that of blood serum.

L. F. Tice

The Merck Manual. Eighth Edition; 1592 pages, incl. index. Merck & Co., Rahway, N. J. Price $4.50; Thumb-Index Edition $5.00.

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